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1: Cell. 2001 Sep 21;106(6):745-57.

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**Cell Press****Structural basis for autoinhibition of the Ephb2 receptor tyrosine kinase by the unphosphorylated juxtamembrane region.****Wybenga-Groot LE, Baskin B, Ong SH, Tong J, Pawson T, Sicheri F.**

Program in Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, 600 University Avenue, Ontario M5G 1X5, Toronto, Canada.

The Eph receptor tyrosine kinase family is regulated by autophosphorylation within the juxtamembrane region and the kinase activation segment. We have solved the X-ray crystal structure to 1.9 Å resolution of an autoinhibited, unphosphorylated form of EphB2 comprised of the juxtamembrane region and the kinase domain. The structure, supported by mutagenesis data, reveals that the juxtamembrane segment adopts a helical conformation that distorts the small lobe of the kinase domain, and blocks the activation segment from attaining an activated conformation. Phosphorylation of conserved juxtamembrane tyrosines would relieve this autoinhibition by disturbing the association of the juxtamembrane segment with the kinase domain, while liberating phosphotyrosine sites for binding SH2 domains of target proteins. We propose that the autoinhibitory mechanism employed by EphB2 is a more general device through which receptor tyrosine kinases are controlled.

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in PubMed Central**cDNA cloning and characterization of eck, an epithelial cell receptor protein-tyrosine kinase in the eph/elk family of protein kinases.****Lindberg RA, Hunter T.**

Molecular Biology and Virology Laboratory, Salk Institute for Biological Studies, San Diego, California 92186-5800.

A human epithelial (HeLa) cDNA library was screened with degenerate oligonucleotides designed to hybridize to highly conserved regions of protein-tyrosine kinases. One cDNA from this screen was shown to contain a putative protein-tyrosine kinase catalytic domain and subsequently used to isolate another cDNA from a human keratinocyte library that encompasses the entire coding region of a 976-amino-acid polypeptide. The predicted protein has an external domain of 534 amino acids with a presumptive N-terminal signal peptide, a transmembrane domain, and a cytoplasmic domain of 418 amino acids that includes a canonical protein-tyrosine kinase catalytic domain. Molecular phylogeny indicates that this protein kinase is closely related to eph and elk and that this receptor family is more closely related to the non-receptor protein-tyrosine kinase families than to other receptor protein-tyrosine kinases. Antibodies raised against a TrpE fusion protein immunoprecipitated a 130-kDa protein that became phosphorylated on tyrosine in immune complex kinase assays, indicating that this protein is a bona fide protein-tyrosine kinase. Analysis of RNA from 13 adult rat organs showed that the eck gene is expressed most highly in tissues that contain a high proportion of epithelial cells, e.g., skin, intestine, lung, and ovary. Several cell lines of epithelial origin were found to express the eck protein kinase at the protein and RNA levels. Immunohistochemical analysis of several rat organs also showed staining in epithelial cells. These observations prompted us to name this protein kinase eck, for epithelial cell kinase.

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